--**Related Applications**

This application is a continuation application of serial no. 09/151,893 filed on September 11, 1998, now abandoned, which is a continuation application of serial no. 08/451,194 filed on May 26, 1995, now U.S. Patent No. 5,833,985, which in turn is a divisional application of serial no. 08/207,344 filed on March 7, 1994, now abandoned. The contents of all of the aforementioned application(s) are hereby incorporated by reference.--

In the Claims:

Please amend claim 28 as follows:

28. (Amended) The bispecific molecule of claim 27, wherein the autocrine growth factor is selected from the group consisting of bombesin and gastrin-releasing peptide.

REMARKS

Claims 25-29 were pending in the application. Claim 28 has been amended to delete reference to GRP receptor binding analogues. No other claims have been amended or canceled. Accordingly, claims 25-29 will be pending upon entry of this Amendment. For the Examiner's convenience, a copy of the claims is set forth herein as Appendix A.

The specification has also been amended to update reference to related applications. Attached hereto is a marked-up version of the changes made to the specification and the claims by the current amendments. The attached page is captioned "Version With Markings to Show Changes Made".

No new matter has been added. The foregoing amendments should in no way be construed as an acquiescence to any of the Examiner's rejections, and have been made solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Priority

The Examiner has indicated that the instant application lacks the necessary references to prior applications as required by 37 C.F.R. 1.62. Accordingly, the specification has been amended to update reference to all prior related applications.

Notwithstanding, Applicants respectfully direct the Examiner's attention to the "Divisional/Continuation Application Transmittal Form" (copy enclosed) submitted upon filing of the instant application (on December 12, 2000). In item number 8 of the Transmittal Form, Applicants requested that the specification be amended to include the necessary references to prior applications.

Rejection of Claim 28 Under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claim 28 under 35 U.S.C. § 112, second paragraph, based on the recitation of the term "analogue." Specifically, the Examiner is of the opinion that the metes and bound of this term are not defined.

Applicants respectfully traverse this rejection for at least the following reasons. However, to expedite prosecution, Applicants have amended claim 28 to delete reference to "analogues" of gastrin releasing peptides.

Notwithstanding, Applicants submit that the term "analogue" is sufficiently clear and definite based on Applicants' description and the state of the art at the time of filing. In particular, at page 3, lines 24-26 of the instant specification, Applicants teach that "[t]he term fragments . . . is intended to include amino acid sequences which differ by one or more amino acid substitutions, additions or deletions from the full length native bombesin or GRP protein . . .." In addition, one of ordinarily skill in the art at the time of filing would have understood that the term "analogue" to mean compound which is structurally similar to a specified compound, and has the same or substantially the same activity as the specified compound, but differs slightly in composition. Accordingly, the term "analogue" is sufficiently definite based on both the definition provided in Applicants' disclosure and the meaning understood in the art.

Moreover, Applicants respectfully note that the term "analogues" was deemed sufficiently definite in the parent application, now issued as U. S. Patent No. 5,833,985 (see, in particular, claims 7 and 8).

Based on at least the above, Applicants respectfully request withdrawal of the rejection of claim 28 under 35 U.S.C. § 112, second paragraph.

Rejection of Claim 28 Under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claim 28 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner is of the opinion that the written description is not commensurate in scope with the claims which read on analogues because the specification only describes GRP and bombesin.

Applicants respectfully traverse this rejection. However, in the interest of expediting prosecution, Applicants have amended claim 28 to delete reference to the term "analogue."

Notwithstanding, Applicants submit that the written description provided in Applicants' specification more than reasonably conveys to the skilled artisan that Applicants were in possession of the claimed invention at the time the application was filed, as required by 35 U.S.C. §112, first paragraph (see M.P.E.P. 2163.02). As noted above, Applicants describe analogues of GRP, including bombesin and other amino acid sequences which differ by one or more amino acid substitutions, additions or deletions from the full length native bombesin or GRP protein, such as allelic variants (page 3, lines 24-26 of the specification). Applicants also describe analogues with various percent homologies to the amino acid sequence of bombesin or GRP (page 3, lines 26-35 of the instant specification). Applicants further describe a method of determining homology between GRP or bombesin and analogues thereof (page 3, lines 35-39 of the instant specification). Thus, Applicants' disclosure provides the requisite evidence that Applicants were in possession of the claimed analogues at the time of filing.

Moreover, Applicants respectfully direct the Examiner's attention to claims 7 and 8 of the issued parent application (US Patent No. 5,833,985), wherein the term "analogue" is recited in a context similar to that in pending claim 28.

For at least the foregoing reasons, Applicants respectfully request withdrawal of the rejection of claim 28 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 25-29 Under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 25-29 under 35 U.S.C. § 112, first paragraph, for lack of enablement. Specifically, the Examiner is of the opinion that "while being enabling for a bispecific molecule comprising bombesin and FcγRI", the specification "does not reasonably provide enablement for any bispecific molecule comprising a growth factor specific for a tumor cell and an antibody or antigen binding fragment."

Applicants respectfully traverse this rejection. Claim 25 is directed to a bispecific molecule comprising an autocrine growth factor specific for a tumor cell and an antibody or antigen binding fragment thereof which binds an Fc receptor of an effector cell at a site that is not inhibited by endogenous immunoglobulin. Dependent claims 26-29 further specify that the tumor cell is a human small-cell lung carcinoma cell; the autocrine growth factor binds to the gastrin-releasing peptide receptor of the human small-cell lung carcinoma cell; the autocrine growth factor is selected from the group consisting of bombesin and gastrin-releasing peptide and gastrin releasing peptide receptor binding analogues thereof; and the Fc receptor is selected from the group consisting of FcγRI, FcγRII and FcγRIII, respectively.

As acknowledged by the Examiner (page 6 of the instant Office Action), the working Examples provided by Applicants in the instant specification fully enable the construction of a bispecific molecule comprising bombesin and an anti-FcγRI antibody. Applicants also provide ample guidance for constructing **any** bispecific molecule encompassed by the claimed invention. For example, Applicants teach at page 5, lines 27 of the instant specification that

> The bispecific molecules of the present invention can be prepared by conjugating (*e.g.* ionically or covalently) the ligand and the antibody or functional antibody fragment using any method known in the art. For example, a variety of coupling or cross-linking agents can be used to covalently conjugate the target cell specific ligand and the effector cell specific antibody. Examples of cross-linking agents include protein A, carboimide, N-succinimidyl-S-acetyl-thioacetate (SATA), N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP), and sulfosuccinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (sulfo-SMCC) (see *e.g.*, Karpovsky *et al.* (1984) *J. Exp. Med.* 160:1686; Liu, M.A. *et al.* (1985) *Proc. Natl. Acad. Sci. USA* 82:8648. Other methods include those described by Paulus (*Behring Inst. Mitt.* (1985) No. 78, 118-132); Brennn *et al.* (*Science* (1985) 229:81-83), and Gennie *et al.* (*J. Immunol.* (1987) 139:2367-2375). Preferred conjugating agents are SATA and sulfo-SMCC, both available from Pierce Chemical Co. (Rockford, IL.).

Thus, Applicants not only exemplify the necessary steps and procedures for constructing the bispecific molecules encompassed by the claimed invention, but also teach additional art-recognized methods and reagents which can be employed in the exemplified steps and procedures to construct any of the bispecific molecules encompassed by the present invention, including a bispecific molecule comprising a growth factor specific for a tumor cell and an antibody or antigen binding fragment which binds to an Fc receptor.

The Examiner asserts that the disclosure fails to provide an enabling disclosure based on the factors set forth in *In re Wands* 858 F.2d 731, 736 (Fed. Cir. 1988) which must be considered when determining whether an undue amount of experimentation is required to practice the claimed invention. These factors include: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the predictability or unpredictability of the art; and (7) the breadth of the claims. Applicants respectfully disagree.

With respect to the Examiner's comments concerning factor 1, *i.e.*, the quantity of experimentation necessary to identify autocrine growth factors, the scientific literature and state of the art at the time of the invention were replete with examples of autocrine growth factors found on tumor cells as well as examples of constructing and using bispecific molecules (See *e.g.*, U.S. Patent No. 4,954,617 issued to Fanger et al. which teaches how to make and use bispecific molecules). Accordingly, minimal experimentation would have been required at the time of filing to identify autocrine growth factors and construct bispecific molecules as claimed by Applicants.

With respect to factor 2, *i.e.*, the amount of direction or guidance presented, the combination of the advanced state of the art at the time of the invention, along with the teachings of Applicants disclosure, clearly provided sufficient guidance for the ordinarily skilled artisan to have practiced the claimed invention without undue experimentation. Indeed, the Examiner acknowledges that the specification enables the construction and use of a bispecific molecule comprising bombesin and anti-FcγRI. The teachings with respect to this bispecific molecule could have been applied to any bispecific molecule in view of the level of skill in the art at the time of filing.

With respect to factor 3, *i.e.*, the presence or absence of working examples, Applicants respectfully point out that the disclosure includes several working examples. The examples illustrate the construction and testing of a bispecific molecule comprising an autocrine growth factor specific for a tumor cell, *i.e.*, bombesin, and an antibody or antigen binding fragment thereof which binds the Fc receptor of an effector cell at a site that is not inhibited by endogenous immunoglobulin, *i.e.*, FcγRI. The Examples further provide *in vitro* data which supports the tumor cell lytic function of the claimed bispecific molecules. It is well-established that enablement does not require *in vivo* data (See *e.g.*, *In re Brana* 51 F.2d 1560, 34 U.S.P.Q.2d (BNA) 1436 (1995). Moreover, as discussed below, the present claims are not drawn to methods of treatment.

With respect to factor 4 and 6, *i.e.*, the nature of the invention and the predictability of the art, the Examiner asserts that there is a great deal of unpredictability associated with cancer treatments. However, Applicants respectfully note that they are not claiming a method of treating cancer. Instead, the present claims are directed to bispecific molecules, the construction and use of which was well-known and predictable in the art at the time of the invention.

With respect to factor 5, *i.e.*, the state of the art, as set forth above, the state of the art with respect to bispecific molecules and growth factors on cancer cells was sufficiently advanced that an ordinarily skilled artisan would have been able to have practiced the claimed invention without undue experimentation.

Finally, with respect to factor 7, *i.e.*, the breadth of the claims, Applicants submit that for all the foregoing reasons, the disclosure is commensurate with the scope of the claims.

In summary, Applicants emphasize that enablement is not precluded by the necessity for some experimentation (see, *e.g.*, *In re Wands* 858 F.2d 731, 736 (Fed. Cir. 1988)). For at least the foregoing reasons, application of the *In re Wands* factors to the presently claimed invention clearly establishes that the claimed bispecific molecules are fully enabled. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 25-29 under 35 U.S.C. § 112, first paragraph.

Double Patenting

The Examiner has rejected claims 25-29 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 of U.S. Patent No. 5,833,985. In particular, the Examiner asserts that, "[t]he prior US Patent No 5,833,985 differs from the instant application in that the instant application recites generic molecules, wherein the molecule claimed in the prior patent, is a specific example. Therefore the claims of a genus are already anticipated."

Applicants respectfully traverse this rejection. However, to expedite prosecution, Applicants will address the double patenting rejection by way of filing a Terminal Disclaimer when the claims in the instant application are indicated otherwise allowable.

Rejection of Claims 25 and 29 Under 35 U.S.C. § 102(a)

The Examiner has rejected claims 25 and 29 under 35 U.S.C. § 102(a) as being anticipated by Shin *et al.* (*J Biol Chem* (Feb.18, 1994) 269(7):4979-4985). Specifically, the Examiner alleges that Shin *et al.* disclose the use of a bispecific molecule which comprises a growth factor, IGF1 or IGF2, and a antibody or antigen binding fragment that binds to a Fc receptor, more specifically FcγRI. The Examiner therefore concludes that the claims of the instant application are anticipated by Shin *et al.*

Applicants respectfully traverse this rejection. Independent claim 25 is directed to a bispecific molecule comprising an autocrine growth factor specific for a tumor cell and an antibody or antigen binding fragment thereof which binds an Fc receptor of an effector cell ***at a site that is not inhibited by endogenous immunoglobulin***. Dependent claim 29 specifies that the Fc receptor is selected from the group consisting of FcγRI, FcγRII and FcγRIII.

Shin *et al.* teach a fusion protein consisting of either rat insulin-like growth factor 1 (IGF1) or human insulin-like growth factor 2 (IGF2) fused to human IgG3. Binding assays performed by Shin *et al.* demonstrated that their IgG3-IGF fusion proteins inhibited the binding of IgG3 to cells (see Figure 5 of Shin *et al.*). Thus, the authors concluded that "the fusion proteins resemble IgG3 in their ability to bind FcγRI" (page 4981, column 2), meaning that the antibody portion of the Shin *et al.* fusion proteins ***competes for binding with endogenous immunoglobulin***.

In contrast, Applicants claim a bispecific molecule comprising an antibody or antigen binding fragment thereof which binds to an Fc receptor of an effector cell ***at a site that is not inhibited by endogenous immunoglobulin***, *i.e.*, a bispecific molecule which does not compete for binding with endogenous immunoglobulin. Accordingly, the Shin *et al.* fusion proteins are structurally distinct from the claimed bispecific molecules.

Accordingly, based on at least the above, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(a) over Shin *et al.*

Rejection of Claims 25-29 Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 25-29 under 35 U.S.C. § 103(a) as being unpatentable over Shin *et al.* (*J Biol Chem* (Feb.18, 1994) 269(7):4979-4985) in view of Cuttita *et al.* (*Nature* (Aug 29, 1985) 316(6031):823-6). Specifically, the Examiner is of the opinion that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to construct a bispecific molecule comprising a bombesin or GRP and an antibody that binds to Fc receptors, because the art teaches that the bispecific molecule as taught by Shin *et al.* was functional and effective and could be used for treating neoplastic disease. In addition it was also taught in the art that small cell lung carcinoma cells express bombesin and GRP and that they acted as growth factors associated with small cell lung carcinoma cells."

Applicants respectfully traverse this rejection. To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been

motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, *e.g.*, *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

Claim 25 is directed to a bispecific molecule comprising an autocrine growth factor specific for a tumor cell and an antibody or antigen binding fragment thereof which binds an Fc receptor of an effector cell at a site that is not inhibited by endogenous immunoglobulin. Dependent claims 26-29 further specify that the tumor cell is a human small-cell lung carcinoma cell; the autocrine growth factor binds to the gastrin-releasing peptide receptor of the human small-cell lung carcinoma cell; the autocrine growth factor is selected from the group consisting of bombesin and gastrin-releasing peptide and gastrin releasing peptide receptor binding analogues thereof; and the Fc receptor is selected from the group consisting of FcγRI, FcγRII and FcγRIII, respectively.

From the outset, even if Shin *et al.* and Cuttita *et al.* were combined in the manner suggested by the Examiner, this would not result in the instantly claimed invention since neither reference teaches or suggests a molecule which binds to an Fc receptor at a site which is not inhibited by endogenous immunoglobulin. Thus, the Examiner has failed to establish even a *prima facie* case of obviousness for the claimed invention.

Notwithstanding, it would not have been obvious to have combined the teachings of Shin Shin *et al.* and Cuttita *et al.* for at least the following reasons. Shin *et al.* teach a fusion protein consisting of either rat insulin-like growth factor 1 (IGF1) or human insulin-like growth factor 2 (IGF2) fused to human IgG3 and an antibody portion which competes for binding with endogenous immunoglobulin, and, thus, which does not bind an Fc receptor of an effector cell at a site that is not inhibited by endogenous immunoglobulin, as claimed by Applicants. Moreover, as acknowledged by the Examiner (pages 9-10 of the instant Office Action), Shin *et al.* fail to teach the bispecific molecules of claims 26-28, namely bispecific molecules wherein the tumor cell is a human small-cell lung carcinoma cell, bispecific molecules wherein the autocrine growth factor binds to the gastrin-releasing peptide receptor of the human small-cell lung carcinoma cell, or bispecific molecules wherein the autocrine growth factor is selected from the group consisting

of bombesin and gastrin-releasing peptide and gastrin releasing peptide receptor binding analogues thereof.

Cuttita *et al.* fail to make up for the deficiency of Shin *et al.* Cuttita *et al.* merely teach that bombesin and bombesin-like peptides (BLPs), such as GRP, can function as autocrine growth factors in human small-cell lung cancer. Cuttita *et al.* fail to anything whatsoever with respect to any bispecific molecules, much less a bispecific molecule as claimed by Applicants. Thus, the ordinarily skilled artisan would ***not*** have been motivated to have tried to substitute the growth factors taught by Cuttita *et al.* in the fusion protein taught by Shin *et al.*. There simply ***was not a sufficient nexus for doing so***. Indeed, in view of the ***vast*** number of other molecules (e.g., ligands and antibodies) that could have been substituted for IGF1 in the fusion construct taught by Shin *et al.*, a *prima facie* case of obviousness in the instant case would require at least ***some*** teaching or suggestion in the prior art for why the particular tumor ligands taught by Cuttita *et al.* should be tried.

It is well established that the motivation, suggestion or teaching of the desirability of making the claimed invention must be founded in the prior art and not in the Applicants' disclosure. *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991). Here, the Examiner has cited a combination of references ***without*** presenting the requisite evidence showing the motivation, suggestion or teaching of the desirability of making the specific combination that was made by the Applicants. Instead, the Examiner has used hindsight (*i.e.*, with the benefit of Applicants' disclosure) to combine references which, at best, ***only teach individual components of the present invention***, since there clearly is ***no nexus*** among the cited references or other reason why one of ordinary skill in the art at the time of the invention would have been motivated to have combined these references in the manner proposed by the Examiner to have arrived at the instantly claimed invention. Thus, the Examiner has failed to establish a *prima facie* case of obviousness.

Accordingly, for at least the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 25-29 under 35 U.S.C. § 103(a).

CONCLUSION

Applicants respectfully submit that the application is now in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the examiner is urged to call Applicants' Attorney at (617) 227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP

Jane E. Remillard, Esq.
Reg. No. 38,872
Attorney for Applicants

28 State Street
Boston, MA 02109
(617) 227-7400

Dated: **November 22, 2002**

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The paragraph beginning at page 1, below the title was replaced with the following:

-- **Related Applications**

This application is a continuation application of serial no. 09/151,893 filed on September 11, 1998, ~~(Pending)~~ now abandoned, which is a continuation application of serial no. 08/451,194 filed on May 26, 1995, ~~(Patented) (~~ now, U.S. Patent No. 5,833,985~~)~~, which in turn is a divisional application of serial no. 08/207,344 filed on March 7, 1994, now abandoned ~~(Abandoned)~~. The contents of all of the aforementioned application(s) are hereby incorporated by reference. –

In the Claims:

Claim 28 was amended as follows:

28. **(Amended)** The bispecific molecule of claim 27, wherein the autocrine growth factor is selected from the group consisting of bombesin and gastrin-releasing peptide ~~and gastrin releasing peptide receptor binding analogues thereof~~.

APPENDIX A

25. A bispecific molecule comprising an autocrine growth factor specific for a tumor cell and an antibody or antigen binding fragment thereof which binds the Fc receptor of an effector cell at a site that is not inhibited by endogenous immunoglobulin.

26. The bispecific molecule of claim 25, wherein the tumor cell is a human small-cell lung carcinoma cell.

27. The bispecific molecule of claim 26, wherein the autocrine growth factor binds to the gastrin-releasing peptide receptor of the human small-cell lung carcinoma cell.

28. **(Amended)** The bispecific molecule of claim 27, wherein the autocrine growth factor is selected from the group consisting of bombesin and gastrin-releasing peptide.

29. The bispecific molecule of claim 25, wherein the Fc receptor is selected from the group consisting of FcγRI, FcγRII and FcγRIII.